

STW



Docket No.: C15043/174944

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :)
Harold M. Bates) Examiner: Not yet assigned
Serial No.: 10/777,543) Expected Art Unit: 1646
Filed: February 12, 2004)
For: DETECTION OF ASYMPTOMATIC)
CORONARY ARTERY DISEASE)
USING ATHEROGENIC PROTEINS)
AND ACUTE PHASE REACTANTS)

FIFTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant wishes to make of record the three documents identified below (clean copies and a Form PTO-1449 listing them are enclosed). **Applicant believes that that no fee is required for this paper** (see last paragraph).

165. Mercodia AB. "Triple-Marker Test"; 4-page brochure (photocopied onto 2 sheets); November 2004.
166. Johnston N, Jernberg T, Lagerqvist B, Siegbahn A, Wallentin L. "Improved Identification Of Patents With Coronary Artery Disease By The Use Of New Lipid And Lipoprotein Biomarkers," *Am J Cardiol.* 2006 Mar 1; 97(5): 640-645; Epub 2006 Jan 10.

167. Johnston N, Jernberg T, Lagerqvist B, Siegbahn A, Wallentin L. "Oxidized Low-Density Lipoprotein As A Predictor Of Outcome In Patients With Unstable Coronary Artery Disease," *Int J Cardiol.* (not yet in print); Epub ahead of print 2005 Dec 7.

REMARKS

The relevance of these items is set forth below.

165. Mercodia AB. "Triple-Marker Test"; 4-page brochure (photocopied onto 2 sheets); November 2004, concerns the use of oxidized low-density lipoprotein as a marker for coronary artery disease ("CAD"). "Oxidized LDL is a more potent and more accurate marker of CAD than the time-honored, conventional blood lipid/lipoprotein biomarkers, particularly total cholesterol, LDL-cholesterol, HDL-cholesterol, and the ratio of cholesterol/HDL." "The ratio of oxidized LDL/HDL-cholesterol – an atherogenic lipoprotein divided by antiatherogenic lipoprotein – is a more potent and more accurate marker of CAD than oxidized LDL." "The Triple-Marker Test is the most powerful trio of biomarkers for distinguishing between CAD patients and non-CAD control subjects. The Triple-Marker Test is a combination of three different biomarkers: oxidized LDL (an atherogenic lipoprotein); HDL-cholesterol (an antiatherogenic lipoprotein); and CRP (an inflammation marker). The Triple-Marker Test result is obtained by multiplying the ratio of oxidized LDL/HDL-cholesterol by CRP. The Triple-Marker Test is more powerful than all of the other biomarkers." Under a bar graph on the second sheet of the photocopy is the following: "The Triple-Marker Test should be useful to clinicians in following the progression of CAD in patients with chest pains since the values of (OxLDL/HDL x CRP) rise progressively from non-CAD (0.2), to stable angina (1.8), to unstable angina (4.4), and to acute myocardial infarction (7.5)."

166. Johnston N, Jernberg T, Lagerqvist B, Siegbahn A, Wallentin L. "Improved Identification Of Patients With Coronary Artery Disease By The Use Of New Lipid And Lipoprotein Biomarkers," *Am J Cardiol.* 2006 Mar 1; 97(5): 640-645; Epub 2006 Jan 10, concerns using OxLDL. "In conclusion, these findings indicate that the ratio of oxidized LDL to HDL cholesterol was a more potent biomarker for discriminating

between subjects with and without coronary artery disease than traditionally measured lipids and lipoproteins and Lp-PLA-2" (Abstract). "A sandwich enzyme-linked Immunosorbent assay was used to measure plasma levels of oxidized LDL (Mercodia AB, Uppsala, Sweden)" (page 641). "The biomarker with the highest diagnostic accuracy in distinguishing healthy controls from patients with coronary artery disease with oxidized LDL/HDL cholesterol" (page 642). ROC curves were used (id.). Monoclonal antibody 4E6 was used (page 642).

167. Johnston N, Jernberg T, Lagerqvist B, Siegbahn A, Wallentin L. "Oxidized Low-Density Lipoprotein As A Predictor Of Outcome In Patients With Unstable Coronary Artery Disease," *Int J Cardiol.* (not yet in print); Epub ahead of print 2005 Dec 7, concerns the prognostic value of circulating oxidized low-density lipoprotein. "Elevated levels of OxLDL may identify patients with unstable CAD, at increased risk for future MI [acute myocardial infarction] independent of other risk variables, particularly those without evidence of myocardial damage. OxLDL levels appear to be similar in patients during the unstable and stable phase of CAD unless statin therapy is initiated." (Abstract) "Plasma levels of OxLDL have been shown to be elevated in patients with established CAD" (page 1). "The present study is the first one to demonstrate that the plasma level of OxLDL may provide important long-term prognostic information in patients with unstable CAD. Patients with OxLDL above the median (76 U/L) had an almost twofold increased risk of suffering from a MI [myocardial infarction] during the following 2 years after an acute coronary event compared to those with lower levels of OxLDL." (page 5) "In this study we found no differences in levels of OxLDL between patients with unstable angina and MI" (id.). "Additionally, we found no relation between other biochemical markers of risk such as CRP, NT-proBNP [N-terminal pro B-type natriuretic peptide] or TnT [Troponin T]. Extensive experimental work has implicated OxLDL as pro-inflammatory." (page 6) "Troponins are sensitive and specific markers of myocardial necrosis. ... When OxLDL was combined with TnT the greatest prognostic value was noted in patients without evidence of myocardial damage whereas no additional predictive value was demonstrated in the TnT positive group." (id.) "In conclusion, in patients with unstable CAD a raised level of OxLDL may be a useful risk marker for MI, especially in patients with normal TnT levels. Statin

therapy appears to reduce levels of OxLDL. Further studies are needed to evaluate the clinical usefulness of our findings." (Id.)

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Document 165 is believed to be among the most relevant of record; documents 166 and 167 are believed to be of lesser relevance; however, the Examiner's independent consideration of these documents and of their relevance is respectfully requested. The Examiner is also requested to initial and return a copy of the accompanying PTO-1449 Form to evidence such consideration.

This FIFTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT is being filed in accordance with the provisions of 37 CFR § 1.97(b)(3) based on applicant's belief that it is being filed before the mailing of a first Office Action on the merits. Thus, **a fee is not required for filing this paper**; however, if any fee is owed, please charge the fee to our Deposit Account No. 02-4467.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on May 24, 2006
(Date of Deposit)

Stephen P. Gilbert
Signature

Respectfully submitted,

Stephen P. Gilbert
Stephen P. Gilbert
Registration No. 27,893

BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104
Phone: (212) 541-2000
Fax: (212) 541-4630

